NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

SCREENING FOR HEMOCHROMATOSIS

GUIDELINES BEING COMPARED

1. **American College of Physicians (ACP)**. Screening for hereditary hemochromatosis: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2005 Oct 4;143(7):517-21. [21 references]
2. **U.S. Preventive Services Task Force (USPSTF)**. Screening for hemochromatosis: recommendation statement. Ann Intern Med 2006 Aug 1;145(3):204-8. [12 references]

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AREAS OF AGREEMENT AND DIFFERENCE

A direct comparison of recommendations presented in the above guidelines for screening for hemochromatosis is provided below.

Areas of Agreement

Routine Genetic Screening

Both ACP and USPSTF found that there is insufficient evidence to support a recommendation for routine genetic screening of the general population for hereditary hemochromatosis. The ACP concludes that the evidence of benefit versus harm is insufficient to support a recommendation either for or against screening. The USPSTF goes a step further and recommends against screening, concluding that the potential harms of genetic screening do, in fact, outweigh the potential benefits.

Potential harms cited by USPSTF include identification of a large number of persons with the high-risk genotype but who may never manifest clinical disease, and related unnecessary surveillance, labeling, anxiety, diagnostic work-ups, and treatments. The ACP guideline notes that potential harms from screening include an adverse impact on insurability and the anxiety of being labeled with a hereditary illness. In addition, because the C282Y mutation does not explain high transferrin saturation and serum ferritin level in nonwhite persons and current research is identifying other genes involved in iron homeostasis, screening for the C282Y mutation could lead to false reassurance in the setting of a negative genetic test result.

In terms of benefits, the USPSTF finds there is only poor evidence that early therapeutic phlebotomy improves morbidity and mortality in screening-detected versus clinically-detected individuals. Similarly, ACP states that available data cannot definitively determine whether phlebotomy will delay or deter the development of cirrhosis (an important morbidity associated with iron overload) over the lifetime of an asymptomatic patient.

Both guidelines agree that prevalence of hereditary hemochromatosis in the general population is low, varies widely between subpopulations, and is highest in white populations. The guidelines further agree that information on the natural history of hemochromatosis is lacking, and this makes it difficult to assess the potential value of early treatment for iron overload. For example, USPSTF points out that even among individuals with mutations on the hemochromatosis gene (HFE), only a small subset will develop symptoms of hemochromatosis and an even smaller proportion of these individuals will develop advanced stages of clinical disease.

Case-Finding

According to ACP, there are no clearly defined criteria to risk-stratify patients into groups that are more or less likely to develop overt disease. However, ACP and USPSTF agree that family members of persons with hereditary hemochromatosis may be more likely to develop symptoms of hemochromatosis; they should be counseled regarding genotyping, and diagnostic testing should be completed as warranted. While USPSTF does not address the nature of further diagnostic testing, ACP recommends that serum ferritin and transferrin saturation tests be performed for case-finding purposes.

Areas of Difference

The USPSTF concludes that the potential harms of genetic screening outweigh the potential benefits and therefore recommends against screening in the general population. The ACP states there is insufficient evidence to determine whether the benefits of screening outweigh the risks; it therefore recommends neither for nor against screening.

COMPARISON OF RECOMMENDATIONS

WHOM TO SCREEN Abbreviations Back to TOC	
ACP (2005)	**Recommendation 1**: There is insufficient evidence to recommend for or against screening for hereditary hemochromatosis in the general population. *There is currently insufficient evidence to determine whether the benefits of screening the general population outweigh the risks. The C282Y mutation is prevalent in certain populations, particularly white men, and treatment is not costly nor is it associated with any significant harm. Although patients homozygous for C282Y are more likely to have elevated serum ferritin level and transferrin saturation percentage, there currently is no way of predicting which patients will progress to overt disease. For clinicians who choose to screen, 1-time phenotypic screening of asymptomatic non-Hispanic white men with serum ferritin level and transferrin saturation would have the highest yield (Adams et al., 2005).*
USPSTF (2006)	The USPSTF recommends against routine genetic screening for hereditary hemochromatosis in the asymptomatic general population. This is a **grade D** recommendation. **Rationale** **Importance**: There is fair evidence that disease due to hereditary hemochromatosis is rare in the general population. **Detection**: The USPSTF found fair evidence that a low proportion of individuals with a high-risk genotype (C282Y homozygote at the HFE locus, a mutation common among white populations presenting with clinical symptoms) manifest the disease. **USPSTF assessment**: The USPSTF concludes that the potential harms of genetic screening for hereditary hemochromatosis outweigh the potential benefits. **Clinical Considerations** This recommendation applies to asymptomatic persons. This recommendation does not include individuals with signs or symptoms that would include hereditary hemochromatosis in the differential diagnosis. Furthermore, it does not include individuals with family history of clinically detected or screening-detected probands for hereditary hemochromatosis. Clinically important disease due to hereditary hemochromatosis

	appears to be rare. Even among individuals with mutations on the hemochromatosis (HFE) gene, it appears that only a small subset will develop symptoms of hemochromatosis. An even smaller proportion of these individuals will develop advanced stages of clinical disease. Screening of family members of probands identifies the highest prevalence of undetected C282Y homozygotes (23% of all family members tested), particularly among siblings (33% homozygosity). **Other Considerations** **System issues**: Genetic screening for hereditary hemochromatosis is not widespread in the United States. **Value**: Systematic screening is potentially costly and may lead to additional diagnostic tests, regular follow-up, and treatment. **Policy issues**: There are important ethical concerns about screening for genetic conditions when the ability to predict the development of disease in those who screen positive is uncertain or very low. Identification of homozygosity could lead to diminished insurability. **Community issues**: While clinical disease associated with hereditary hemochromatosis is uncommon, there is significant variation in the prevalence of C282Y homozygotes according to race and ethnicity.
SCREENING METHODS AND TOOLS Abbreviations Back to TOC	
ACP (2005)	**Recommendation 2**: In case-finding for hereditary hemochromatosis, serum ferritin and transferrin saturation tests should be performed. *There is no information available on risk-stratifying in patients with an associated condition or conditions such as type 2 diabetes, cardiac arrhythmias and cardiomyopathies, liver failure, hepatomegaly, cirrhosis, elevated liver enzyme levels, hepatocellular carcinoma, arthritis, hypogonadism, or changes in skin pigmentation. The initial symptoms associated with iron overload might be nonspecific, and the decision to perform tests should be based on clinical judgment regarding what may cause such protean manifestations. If testing is performed for these patients, the cutoff values for serum ferritin level of more than 200 micrograms/L in women or more than 300 micrograms/L in men and transferrin saturation greater than 55% may be used as criteria for case-finding; however, there is no general agreement about*

	diagnostic criteria. Case-finding may also be considered if there is a family history of hereditary hemochromatosis for an individual, as the risk for developing the disease may be higher than that of the general population.
USPSTF (2006)	No recommendations offered. **Accuracy of Screening Tests** Because of the targeted nature of this review, the USPSTF did not focus on the accuracy of genetic screening tests. Nor did the USPSTF assess the validity of various combinations of phenotypic and genotypic approaches to screening. Rather, the USPSTF focused on genetic screening for hereditary hemochromatosis, specifically C282Y homozygosity. The USPSTF did not assess the role of increased serum iron measures such as transferrin saturation and serum ferritin in screening. While elevated serum iron measures may provide more "clinically" relevant information about early disease, the predictive value for progression of disease is limited (Andersen et al., 2004). **Clinical Considerations** In addition to genotyping, more common laboratory testing can sometimes identify iron overload. Clinical screening with these laboratory tests, or phenotypic screening, was not included in the evidence synthesis on which this recommendation [see Recommendation 1 above] is based. Genotyping primarily focuses on the identification of the C282Y mutation on HFE. While other mutations exist, C282Y homozygosity is most commonly associated with clinical manifestations. Identifying an individual with the genotypic predisposition does not accurately predict the future risk for disease manifestation.
PATIENT AND FAMILY MEMBER EDUCATION/COUNSELING **Abbreviations** **Back to TOC**	
ACP (2005)	**Recommendation 3**: Physicians should discuss the risks, benefits, and limitations of genetic testing in patients with a positive family history of hereditary hemochromatosis or those with elevated serum ferritin level or transferrin saturation. *Before genetic testing, individuals should be made aware of the benefits and risks of genetic testing. This should include discussing available treatment and its efficacy; costs involved (Beutler et al., 2002); and social issues, such as impact of disease labeling, insurability and psychological well-being, and the possibility of as-yet-unknown genotypes associated with hereditary hemochromatosis.*

USPSTF (2006)	No recommendation offered. **Clinical Considerations** Individuals with a family member, especially a sibling, who is known to have hereditary hemochromatosis may be more likely to develop symptoms. These individuals should be counseled regarding genotyping, with further diagnostic testing as warranted as part of case-finding.

STRENGTH OF EVIDENCE AND RECOMMENDATION GRADING SCHEMES **Abbreviations** **Back to TOC**	
ACP (2005)	The recommendations are supported by data from cohort, cross-sectional, and case-control studies.
USPSTF (2006)	The U.S. Preventive Services Task Force grades the **quality of the overall evidence** for a service on a 3-point scale (good, fair, poor): **Good** Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes. **Fair** Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes. **Poor** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes. **Strength of Recommendations** The USPSTF grades its **recommendations** according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

	A The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms. **B** The USPSTF recommends that clinicians provide [this service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms. **C** The USPSTF makes no recommendation for or against routine provision of [the service]. The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation. **D** The USPSTF recommends against routinely providing [the service] to asymptomatic patients. The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits. **I** The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.

COMPARISON OF METHODOLOGY ***Click on the links below for details of guideline development methodology***	
ACP **(2005)**	**USPSTF** **(2006)**
Both organizations performed a systematic review of the literature that included applying quality criteria to published studies to select those suitable for evidence review and guideline formulation. The USPSTF systematic review document (see "Availability of Companion Documents" in the NGC summary of this guideline) provides quality rankings for included studies and provides reasons for rejection of	

excluded studies. In addition, its recommendation statement grades the strength of the evidence that supports its recommendation. The ACP systematic review document (see "Availability of Companion Documents" in the NGC summary of this guideline) lists in table format the methodologic or quality issues of the studies that were considered by ACP in answering each of five key questions concerning screening for hemochromatosis. Although ACP does not explicitly rank the quality of studies reviewed or the strength of the evidence behind each recommendation, it discusses the strength of the evidence in narrative format.

SOURCE(S) OF FUNDING **Abbreviations** **Back to TOC**	
ACP (2005)	American College of Physicians
USPSTF (2006)	United States Government

BENEFITS AND HARMS **Abbreviations** **Back to TOC**	
Benefits	
ACP (2005)	• Appropriate screening for hereditary hemochromatosis in light of efficacy of available treatment and value of detecting individuals who are homozygous for the mutation but may not develop iron overload • Serum ferritin level and transferrin saturation have been useful in identifying patients who are prone to or already have hereditary hemochromatosis
USPSTF (2006)	Appropriate screening for hereditary hemochromatosis in primary care settings
Harms	
ACP (2005)	• The value of detecting individuals who are homozygous for the mutation but do not develop iron overload is controversial. The psychological and social implications of identifying such individuals must be considered. Issues such as the impact on insurability and

	the anxiety of being labeled with a hereditary illness need to be considered when comparing the benefits and risks of screening. • False reassurance in the setting of a negative genetic test result is not unreasonable.
USPSTF (2006)	• Screening could lead to identification of a large number of individuals who possess the high-risk genotype but may never manifest the clinical disease. This may result in unnecessary surveillance, labeling, unnecessary invasive work-up, anxiety, and, potentially, unnecessary treatments. • Harms associated with screening are not well studied. Potential harms include the psychological burden of being labeled as having a chronic disease, the potential consequence of this labeling on a person's ability to obtain health or life insurance, and concern associated with genetic testing in the absence of qualified genetic counseling. Phlebotomy, a somewhat invasive procedure, is associated with some harms.

Abbreviations
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ACP, American College of Physicians

EPC, Evidence-based Practice Center

HFE, the hemochromatosis gene

USPSTF, U.S. Preventive Services Task Force

This Synthesis was prepared by ECRI on March 26, 2007. The information was verified by ACP on June 25, 2007.

Internet citation: National Guideline Clearinghouse (NGC). Guideline synthesis: Screening for hemochromatosis. In: National Guideline Clearinghouse (NGC) [Web site]. Rockville (MD): 2007 Jul. [cited YYYY Mon DD]. Available: http://www.guideline.gov.

Date Modified: 5/3/2010